rates in hepatocellular carcinoma (HCC), which has been attributable to the strong immunosuppressive tumor microenvironment (TME). As a key player in the TME, myeloid-derived suppressor cell (MDSC) shows potent T cell-suppressive activity that remarkably associates with poor prognosis and ICB resistance of cancer patients. While targeting MDSC can blunt T cell activity, a new approach is directed towards driving MDSC differentiation into antigen presentation cell crucial for T cell priming and activation. We have recently shown that hepatoma-intrinsic cyclin-dependent-kinase 20 (CDK20), or cell-cycle-related-kinase (CCRK) depletion diminishes MDSC-mediated immunosuppression leading to improved ICB efficacy (*Gut* 2018). As emerging evidence highlights the key roles of immune cell-intrinsic CDKs, we aimed to further explore the potentials of CCRK in immune cell identity.

Methods The expression profile of CCRK was determined in flow-sorted immune cells from tumor-bearing mice and HCC patients. Functional significance and molecular mechanisms of CCRK in MDSCs were conducted by gene knockdown in human blood-derived MDSCs, followed by mRNA and protein detection, qChIP-PCR and multi-colour flow cytometry. The MDSC differentiation and T cell suppression in tumorigenicity were validated in HCC mouse model with intratumoral MDSC injection.

Results We uncovered specific over-expression of CCRK in MDSCs but not lymphocytes from tumor-bearing mice and HCC patients. Notably, blockade of MDSC-intrinsic CCRK induced its differentiation into antigen-presenting macrophage, which amplified T cell responses in vitro and in vivo, resulting in reduced tumorigenicity. CCRK inhibition suppressed signal transducer and activator of transcription 3 (STAT3) signaling to revert E4-binding protein 4 (E4BP4)-dependent interleukin-10 (IL-10)/IL-12 imbalance and arginase I expression, thus blunting immunosuppression.

Conclusions Our findings demonstrate that targeting myeloid-intrinsic CCRK signal can amplify anti-tumor T cell responses. As we also showed CCRK overexpression in patient-derived MDSCs, our results not only unravel mechanistic insights in MDSC identity but also offer a novel therapeutic kinase-target for a combinational immunotherapy strategy for conferring durable eradication of solid tumors.

IDDF2020-ABS-0182 A NOVEL IMMUNOSUPPRESSIVE ROLE OF CHOLESTEROL IN NAFLD-ASSOCIATED HEPATOCARCINOGENESIS

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Background Hepatocellular carcinoma (HCC) is the fifth most prevalent cancer and the second leading cause of cancer deaths worldwide. Driven by the epidemics of obesity and diabetes, it is anticipated that non-alcoholic fatty liver disease (NAFLD) will become the most important cause of HCC. Emerging evidence suggests that metabolic and immune dysfunction are key features of NAFLD-associated HCC, my research aim to investigate the metabolic-immune dysregulation underlying NAFLD-HCC development. Here we show that aberrant cholesterol accumulation in the liver predisposes cancer development by reprogramming the immunosurveillance microenvironment.

Methods Comprehensive immune profiling in a high-fat high-carbohydrate diet-induced NAFLD murine model was performed.

Results Our results revealed a specific reduction of cytolytic natural killer T (NKT) cells in the liver, which was negatively correlated with the elevated cholesterol level. Cholesterol-lowering drug Rosuvastatin reduced cholesterol level and restored NKT cell proportion and function, which subsequently suppressed the growth of orthotopically-implanted HCC tumor. Inhibition of cholesterol synthesis by an mTORC1/C2 dual kinase inhibitor Vistusertib (AZD2014), or lentiviral-mediated suppression of the mTOR pathway also showed similar effects. Notably, NKT inactivation by a specific CD1d receptor-targeting antibody abolished the anti-tumorigenic effects of both Rosuvastatin and Vistusertib, thus underscoring the casual role of NKT in cholesterol-mediated hepatocarcinogenesis. We also showed a reduction of NKT cells and its negative correlation with cholesterol elevation in obese patients undergone bariatric surgery.

Conclusions Our study elucidates a new immunosuppressive role of cholesterol in establishing a pro-tumorigenic microenvironment. These findings explain why cholesterol-lowering drugs may reduce cancer incidence and provide new therapeutic strategies of revitalizing the immunosurveillant NKT cells for the intervention of NAFLD-associated HCC.

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IDDF2020-ABS-0201 TARGETING HEPATOMA-INTRINSIC PPARγ SIGNALING OVERCOMES IMMUNE CHECKPOINT THERAPY RESISTANCE BY INFLAMING THE TUMOR MICROENVIRONMENT

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Background Immune-checkpoint blockade (ICB) therapies by antibodies against programmed death 1 (PD1)/PD1 ligand 1 (PD-L1) axis have revolutionized the treatment paradigm for cancer. Although subsets of people exhibit durable responses, ICB resistance has increasingly been observed, especially in hepatocellular carcinoma (HCC). Here we utilized a single-cell RNA-sequencing (scRNA-seq) approach to elucidate the tumor-intrinsic mechanism underlying tumor immunosuppression and ICB resistance.

Methods We first recapitulated the clinical outcome of ICB resistance via repeated cycles of in vivo selection in orthotopic murine models of HCC. To investigate the tumor cell-extrinsic resistant factors, the myeloid and lymphoid immune populations were profiled by multi-color flow cytometry. To dissect hepatoma-intrinsic resistant signatures, we performed scRNA-seq from anti-PD-L1-treated tumors generated from parental or PD-L1R Hepa1-6 cells. The anti-tumor efficacy and immunophenotype of combined therapy with anti-PD-L1 antibody